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March 3, 2003

Via Express Mail No.: EV 244879067 US
Commissioner for Patents
Washington, D.C. 20231

Re: Public Protest Against U.S. Serial No. 09/724,406
Under 37 CFR § 1.291

Dear Sir:

Enclosed herewith for filing in the above-referenced matter, please find the following:

(1) Public Protest Against U.S. Serial No. 09/724,406 Under 37 CFR § 1.291;

(2) Pohl et al. (1993) Int. J. Cancer 54:418-425 reference;

(3) Certificate of Service; and

(4) Acknowledgment Postcard.

Please note that a true copy of this Public Protest Against U.S. Serial No. 09/724,406 Under 37 CFR §1.291 has been served on counsel for Seattle Genetics, Inc. by Express Mail, mailing label number EL 833313873 US, postage prepaid at Boston, Massachusetts, to Adriane M. Antler, Esquire, Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036.

"Express Mail" mailing label number EV 244 879 067 US

Date of Deposit March 3, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Washington, D.C. 20231

Signature

Viriato G. Cardoso
Please Print Name of Person Signing

Respectfully submitted,

Jane E. Remillard, Esq.
Reg. No. 38,872

JER:mdm
Encs.

CERTIFICATE OF SERVICE

I, Jane E. Remillard, Esquire, hereby certify that a true copy of this Public Protest Against U.S. Serial No. 09/724,406 Under 37 CFR §1.291 has been served on counsel for Seattle Genetics, Inc. by Express Mail, mailing label number EL 833313873 US, postage prepaid at Boston, Massachusetts, to Adriane M. Antler, Esquire, Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036.

Jane E. Remillard, Reg. No. 38,872

Dated: March 3, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of: Francisco, Joseph A. et al.

U.S. Serial No: 09/724,406

Filing Date: November 28, 2000

Title: *RECOMBINANT ANTI-CD30 ANTIBODIES AND USES THEREOF*

Commissioner for Patents
Washington, D.C. 20231

PUBLIC PROTEST AGAINST U.S. SERIAL NO. 09/724,406

UNDER 37 CFR § 1.291

#19 6-4-03

The above-identified U.S. patent application, U.S. Serial No. 09/724,406 (the '406 Application), is hereby protested in view of the following reference: Pohl *et al.*, (1993) *Int. J. Cancer* 54:418-425. It is noted that the Pohl reference was published in 1993, more than one year before the filing date of the '406 Application and, thus, is available as prior art under 35 U.S.C. §102(b). For the Examiner's convenience, a copy of both the '406 Application[1] and the Pohl reference are enclosed.

The '406 Application claims a method for treating or preventing Hodgkin's Disease (HD) by administering anti-CD30 antibodies that exert a cytostatic or cytotoxic effect on HD cells. The '406 Application further claims pharmaceutical compositions containing such antibodies. Representative method and pharmaceutical compositions claims in the '406 Application are shown below, corresponding to claims 1 and 20 of the '406 Application as originally filed.

[1] The enclosed copy of the '406 Application serves as the priority document for PCT Publication WO 02/43661 (a continuation-in-part application of the '406 Application) and was obtained as part of the published file history for WO 02/43661.

Exemplary method claim

A method for the treatment or prevention of Hodgkin's Disease in a subject comprising administering to the subject, in an amount effective for said treatment or prevention, (a) an antibody that (i) immunospecifically binds CD30 and (ii) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line; and (b) a pharmaceutically acceptable carrier.

Exemplary composition claim

A pharmaceutical composition comprising:

(a) an antibody that (i) immunospecifically binds CD30 and (ii) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, and is not monoclonal antibody AC10 or HeFi-1 and does not result from cleavage of AC10 or HeFi-1 with papain or pepsin, in an amount effective for the treatment or prevention of Hodgkin's Disease; and

(b) a pharmaceutically acceptable carrier.

As discussed in detail below, the Pohl reference teaches the methods and compositions claimed in the '406 Application. Specifically, Pohl *et al.* describe studies utilizing monoclonal antibodies that: (i) bind to CD30 and (ii) exert a cytostatic or cytotoxic effect on a HD cell line. The antibodies described by Pohl *et al.* are not AC10 or HeFi-1, nor are they derived from AC10 or HeFi-1. Still further, Pohl *et al.* showed that the antibodies, formulated into pharmaceutical compositions, can be used to treat HD in animal models. Indeed, the authors explicitly state in the abstract that "[m]onoclonal [anti-CD30] Ab3 4A4 was cytotoxic for $CD30^+$ cell lines *in vitro* and effectively prevented the s.c. growth of L540 cell tumors after passive i.v. administration in

a SCID mouse tumor model." (emphasis added) Therefore, it is respectfully requested that the Examiner consider the Pohl reference and arguments below with regard to patentability of the invention(s) claimed in the '406 Application and related applications.

Summary of Pohl *et al.* and its relevance to the '406 Application

I. Pohl *et al.* describe monoclonal antibodies that specifically bind to CD30

Pohl *et al.* describe two different monoclonal antibodies (mAbs) that bind to CD30, referred to as mAbs HRS-4 (Ab1) and 4A4 (Ab3), which they used to demonstrate the efficacy of a vaccine therapy (based on anti-idiotypic antibodies) to treat HD. More specifically, they used a previously-known anti-CD30 monoclonal antibody named HRS-4, which they also refer to as Ab1, to generate an anti-idiotypic monoclonal antibody named 9G10, which they also refer to as Ab2. The authors hypothesized that this anti-idiotypic antibody (Ab2) mimics the conformation of the CD30 antigen, and thus could be used in vivo as a CD30 antigen vaccine to induce additional antibodies that would bind CD30, thereby inducing a protective CD30-specific response in the absence of the nominal CD30 antigen. Thus, Pohl *et al.* used the 9G10 monoclonal (Ab2) to raise another monoclonal antibody named 4A4, which they also refer to as Ab3. Like HRS-4, the Ab3 also was shown to bind CD30.

The HRS-4 (Ab1) and 4A4 (Ab3) antibodies share similar binding specificity for CD30. As stated by Pohl *et al.* (page 421, col. 1, last paragraph to col. 2, first paragraph),

> [t]o test whether Ab3 represents a true internal image of Ab1 HRS-4 with specificity for CD30, binding with CD30-positive and CD30-negative cell lines was examined by FACS analysis. As shown in Figure 4, Ab3 bound avidly, although to a lesser extent than HRS-4, to the $CD30^+$ cell line L540, while no binding to the $CD30^-$ cell line HPB-ALL was observed. This binding was specific, since unrelated IgM showed no binding. Similar results were found on a

variety of $CD30^+$ and $CD30^-$ cell lines, as summarized in Table I. These data suggested that Ab3 4A4 and Ab1 HRS-4 have a similar binding site to CD30 antigen.

II. The anti-CD30 mAbs of Pohl *et al.* exert cytostatic and cytotoxic effects on a Hodgkin's Disease cell line

Pohl *et al.* performed both *in vitro* and *in vivo* experiments to demonstrate that the 4A4 (Ab3) and HRS-4 (Ab1) anti-CD30 mAbs have cytostatic and/or cytotoxic effects on L540 (HD) tumor cells. Specifically, the authors tested these mAbs for complement-dependent cytotoxicity (CDC) *in vitro*, antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro* and prevention of tumor growth *in vivo*. In the *in vitro* studies, mAb 4A4 (Ab3) was shown to exert a cytotoxic effect on L540 cells. In particular, Pohl *et al.* state that "[a]s shown in Figure 8, a 28% specific lysis of $CD30^+$ cells was induced by monoclonal IgM-Ab3 4A4, whereas unrelated IgM induced only about 10% lysis" (page 422, col. 1, paragraph 2).

In the *in vivo* tumor model, mAb 4A4 (Ab3) also inhibited the growth of HD tumor cells. Pohl *et al.* injected 150 μg of 4A4 (Ab3), formulated with a pharmaceutically acceptable carrier (PBS), into the tail vein of SCID mice followed (1 hour) by injecting L540 cells s.c. at the ventral thoracic wall to induce solid HD tumors (see p. 422, right column). Figure 10a shows that no palpable tumor was detected in animals treated with mAb 4A4 (Ab3) at least 32 days after tumor challenge, while untreated mice developed HD tumors (see p. 422, right column). Moreover, the mAb HRS-4 (Ab1) also was tested in the study, and was shown to exert the same effect on inhibiting HD tumor growth as mAb 4A4 (Ab3). Accordingly, the results of this *in vivo* experiment demonstrated that these anti-CD30 mAbs exerted a cytostatic or cytotoxic effect on HD tumor cells *in vivo* and can be used to prevent and treat HD. Furthermore, these experiments demonstrated that an anti-idiotype antibody (Ab2), which was raised against a first

anti-CD30 antibody (HRS-4; Ab1), can generate another anti-CD30 antibody (4A4; Ab3) that mimics the internal image of Ab1, binds to CD30 in a similar manner as Ab1, and exerts a cytostatic or cytotoxic effect on HD tumor cells.

The '406 Application

The '406 Application claims a method for using an anti-CD30 mAb to treat or prevent HD, as well as pharmaceutical compositions containing an anti-CD30 mAb (see, *e.g.*, Exemplary claims, *infra*). The '406 Application specifically describes two murine mAbs that bind CD30, *i.e.*, AC10 (a.k.a. C10) and HeFi-1, which were both previously described in the prior art and shown to bind CD30 (see, *e.g.*, Bowen et al., 1993, *J. Immunol.* 151: 5896-5906 and Hect *et al.*, 1985, *J. Immunol.* 134:4231-36). In addition, the '406 Application contains data from *in vivo* experiments, including injecting the prior art antibodies AC10 or HeFi-1 i.p. into SCID mice bearing disseminated HD (L540) tumor cells.

Based on the teachings in the Pohl reference, a claim to a method for using a monoclonal antibody that binds CD30 and exerts a cytostatic or cytotoxic effect on HD cells to treat or prevent HD, as claimed in the '406 application, is clearly anticipated. Similarly, a claim to a pharmaceutical composition containing such an anti-CD30 mAb, or containing such an anti-CD30 mAb that "is not monoclonal antibody AC10 or HeFi-1" (see *e.g.*, claim 20) is also clearly anticipated. Indeed, the Pohl reference teaches anti-CD30 antibodies, other than AC10 and HeFi-1 that specifically bind to CD30. The reference further demonstrates, through both *in vitro* and *in vivo* studies, that such antibodies exhibit cytostatic or cytotoxic effects on $CD30^+$ tumor cells and can be used to prevent HD tumor formation or treat HD *in vivo*.

Similarly, the added claim limitation, whereby the anti-CD30 antibody is conjugated to a cytotoxic agent, in certain dependent claims of the '406 Application (see *e.g.*, claim 4), is not novel. Indeed, at page 2 (lines 8-10) of the '406 Application, the Applicants explicitly acknowledge that it was shown in earlier clinical trials that "a toxin (saporin) was chemically conjugated to the antibody BerH2 [an anti-CD30 mAb] and all four patients demonstrated rapid and substantial reductions in tumor mass (Falini *et al.,* (1992) *Lancet* 339:1195-1196)."

Moreover, the additional dependent claim limitations reciting, for example, that (i) the antibody is "human, humanized or chimeric" (see *e.g.*, claim 2), that (ii) chemotherapy is administered (see *e.g.*, claim 3), that (iii) the antibody is fused to a second protein which is not an antibody (see *e.g.*, claim 5), that (iv) the cytotoxic or cytostatic effect is determined by a particular thymidine incorporation assay (see e.g., claim 7), or that (v) the Hodgkin's Disease cell line is L428, L450, HDLM2 or KM-H2 (see *e.g.*, claim 37), are all obvious in view of the Pohl *et al.* reference. These limitations encompass known technologies available in the art at the time of the filing of the '406 Application.

Related Applications

Although this protest is filed against the '406 Application, the arguments presented herein regarding the teachings of the Pohl *et al.* reference are equally applicable to applications related to the '406 Application that similarly claim methods of using, or compositions containing, antibodies that bind to CD30 and exert a cytostatic or cytotoxic effect on HD tumor cells. Thus, this protest is also made against such related applications, if pending. For example, a continuation-in-part application of the '406 Application has been published as PCT Publication WO 02/43661, which PCT application designates the United States. Claim 1 of WO 02/43661 recites (emphasis added):

A method for the treatment or prevention of Hodgkin's Disease in a subject comprising administering to the subject, in an amount effective for said treatment or prevention, (a) an antibody that (i) immunospecifically binds CD30 and (ii) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein said antibody exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent, respectively; and (b) a pharmaceutically acceptable carrier.

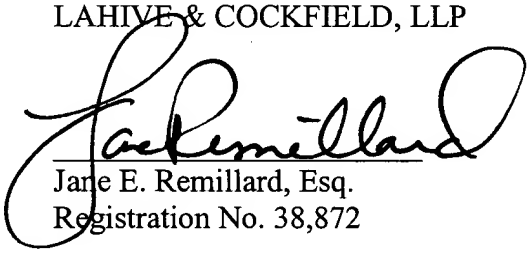
From the outset, it is noted that the underlined phrase does not find support in the '406 Application. Thus, a claim in any U.S. application corresponding to claim 1 of WO 02/43661 would not be entitled to the priority date of the '406 Application. Moreover, as discussed above, it is noted that the underlined phrase does not impart novelty over the Pohl *et al.* reference since Pohl *et al.* clearly teach anti-CD30 antibodies (*i.e.*, HRS-4 and 4A4) which exert a cytostatic or cytotoxic effect on HD cells in the absence of conjugation to a cytostatic or cytotoxic agent.

CONCLUSION

Based on the foregoing, it is respectfully requested that the Examiner of the '406 application, and any related applications, consider the Pohl *et al.* reference, along with the present protest, during examination. For at least the reasons provided above, it is respectfully concluded that the claims of the '406 application are not patentable over the Pohl *et al.* reference.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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